



CASE: LA0112 NP

CERTIFICATE OF MAILING

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Burton Rodney
Type or print name

Signature

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

ART UNIT: 1626

TIMUR GUNGOR, ET AL.

EXAMINER: STOCKTON, LAURA LYNNE

APPLICATION NO: 10/775,742

FILED: 02/10/2004

FOR: NOVEL THIAZOLIDINE COMPOUNDS AS CALCIUM
SENSING RECEPTOR MODULATORS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF HAO ZHANG

To the Commissioner for Patents and Trademarks:


HAO ZHANG DECLARES AS FOLLOWS:

1. He has a Master's degree and is a chemist specializing in preparation of organic compounds.
2. He was employed in the above capacity at Bristol-Myers Squibb Company for more than 9 years.
3. He is familiar with the laboratory experiments carried out by Ying Chen concerning preparation of chemical compounds.

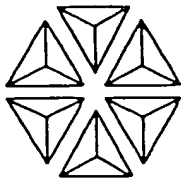
4. He signed as a witness laboratory notebook entries made by Ying Chen in Notebook No. 48255, pages 101, 102, 103, 104, 105 and 108 (ATTACHMENT C, cover page, and ATTACHMENTS D, E, F, G, H and I', respectively).
5. All of the above notebook pages were signed by Ying Chen prior to October 22, 2001.
6. All of the above notebook pages were witnessed by him prior to October 22, 2001.
7. He is not an inventor of the subject matter claimed in U.S. Application Serial No. 10/775,742.
8. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of application Serial No. 10/755,742 or any patent issued thereon.

Date:

9/25/56


HAO ZHANG

PROPERTY OF
BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE



BRISTOL-MYERS SQUIBB

NOTEBOOK No. 48255

Ying Chen
AMGEN

Assigned to *Ying Chen*

Subject _____

Department Name _____

Department Number _____

Date Assigned *1-6*

Date Completed _____

Pages Completed from _____ to _____

Continued from Notebook Number _____

Continued in Notebook Number _____

This notebook cannot be transferred to another person

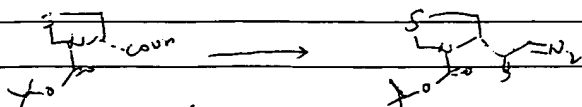
ATTACHMENT C

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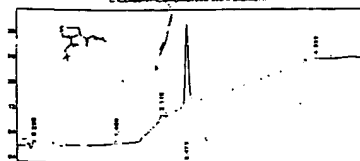
5	Boc-D-thiazolidine-4-carboxylic acid	5.0 g	21.4 mmol
	isobutylchloroformate	2.76 ml	21.4 mmol
	Et ₃ N	30 ml	21.4 mmol
	THF	50 ml	
	MNNG	11.7 g	
10	KOH/H ₂ O	153 in 37 ml	
	Et ₂ O	125 ml	

To a two phase solution of KOH and Et₂O at 0°C was added MNNG portionly. The ether layer was decanted to a flask. The flask made CH₂ in Et₂O was kept at 0°C. To a solution of Boc-D-thiazolidine-4-carboxylic acid, Et₃N in THF at -10°C (acetone + ice) was added dropwise isobutylchloroformate. The reaction was kept at -10°C for 30 min then filtered (white solid was resulted from Et₃N.HCl). The filtrate was stirred at -10°C. A solution of CH₂ in Et₂O was added. Stirring was continued for 1h. Then warmed to RT. Et₂O was added and the solution washed with H₂O, Satd NaHCO₃ brine and dried over MgSO₄. Evaporation gave a yellow oil. Purification was performed by flash column on silica gel, loaded with CH₂Cl₂. Eluted with 25% Et₂O in hexane. Pure fractions were combined and evaporated to give a pale yellow oil.

25. 48255-101
C:\CLASS-VOL\48255-101-27

Instrument = HPLC-1027-10MS1
Well = 192 Inj. Vol. = 10 µl
Start = 0
Final = 100
Gradient Time = 4 min
Flow Rate = 1 ml/min
Wavelength = 220
Solvent A = 10% MeOH - 90% H₂O - 0.3% TFA
Solvent B = 90% MeOH - 10% H₂O - 0.3% TFA
Column 2 = Phenomenex ODS 4.6 x 50 mm 14 min

48255-101



RT	Area	Area %	Placed
12.5	31325	3.367	161
12.7	27629	2.946	2134
12.9	55862	6.084	7273
13.1	455927	49.081	11713
13.3	559915	60.462	8

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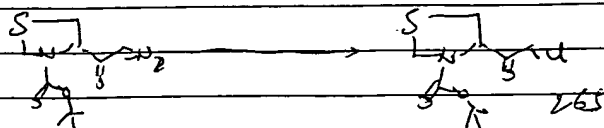
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SUBJECT



5

4.4 g

5 ml

10 ml

10

To a solution of 48255-101-27 in CH₂Cl₂ at -10°C, a solution of 48255-101-27 in CH₂Cl₂ was added dropwise. (A lot of bubbles). The reaction was stirred at -10°C for 30 min. HCl was evaporated by a vacuum pump without heating. The rest of solution was warmed to RT. Evaporation was without heat to give a yellow oil. 4.4g

IF255-10274

15

CC-MS mpv = 288

HWmk were consistent

 $^{13}\text{CH}_2\text{MP}$

RQ 22935. 7K2723f M-1 = 263.9

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ATTACHMENT E

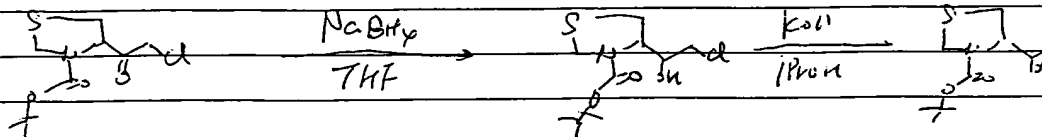
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5

48255-102-14

4.4 g

16.6 mmol

NaBH₄

614 mg

16.6 mmol

THF

30 ml

10

To a solution of 48255-102-14 in THF at RT was added NaBH₄. The reaction was stirred at RT for 30 min. LC-MS showed 2 SM left. H₂O was added to quench the reaction. EtOAc was added and the solution was washed with sat'd NaHCO₃, brine and dried over MgSO₄. Evaporation gave a crude oil. 48255-103-13

LC-MS showed right M+23 = 290 two isomer ratio 3:1

15

To a solution of 48255-103-13 in PhOH (10 ml) was added K₂CO₃ (10 ml). The mixture was stirred at RT for 1 h. EtOAc was added and the organic layer was washed with sat'd NaHCO₃, brine and dried over MgSO₄. Evaporation gave a crude oil. 48255-103-18

¹H NMR showed two isomer ratio = 2:1

20

Purification was performed by flash chromatography on silica gel, loaded with crude, eluted with 8% EtOAc in hex. Pure fractions were combined and evaporated to give a colorless oil 48

Isomer I 48255-103-23 1.2 g

¹H NMR and ¹³C NMR were consistent.

25

IR 2305, 1727, 1738 MS: M+1 = 232.

Isomer II 48255-103-27 1.6 g

IR 2305

IR 2739 M+1 = 232

30

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ATTACHMENT F

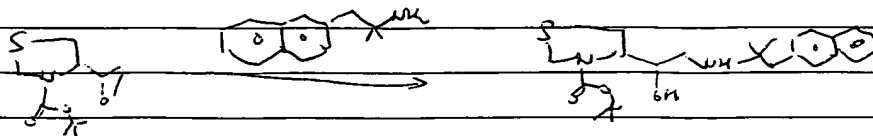
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SUBJECT _____



5

48255-103-23

500 mg

2.17 mmol

Amine

432 mg

2.17 mmol

The mixture of 48255-103-23 and amine was heated together at 90°C for 3 hr. TLC and LC-MS showed no epoxide left. The reaction was cooled to RT. Purification was performed by flash chromatography on silica gel, loaded with column, eluted with 3% MeOH in CH₂Cl₂ + 0.1% NH₄OH. Pure fractions were combined and evaporated to give a colorless oil.

10

48255-100-1K 833 mg (87%)

KQ23057 BMS-538174-01

15

MS (TR 273.84) m+1 = 431

1H NMR

13C NMR

were consistent.

20

Analytical HPLC Report

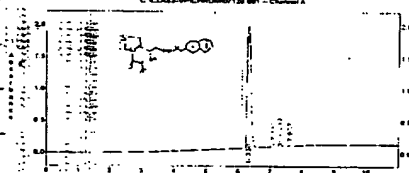
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7:24:31

Instrument: NPM-L132-HPLC
 Well: 177 Inj. Vol.: 10 µL
 Start: 0 min Final: 100 min
 Gradient Time: 8 min
 Flow Rate: 2.5 ml/min
 Wavelength: 210 nm
 Solvent A: 10% MeOH - 90% H₂O - 0.2% H₃PO₄
 Solvent B: 90% MeOH - 10% H₂O - 0.2% H₃PO₄
 Column 1: Zorbax SB-C18 4.6mm ID x 75mm (8 min)

48255-100-1K

25



Channel A Results

Peak	RT	Area	Area %	Height
1	7.23	7622796	96.697	16497
2	7.31	76189	0.943	90392
3	7.23	152876	1.939	90799
4	7.24	31342	0.394	71777

30

7683122 100.000

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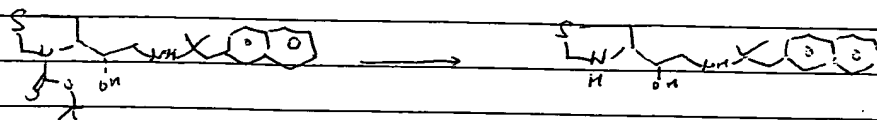
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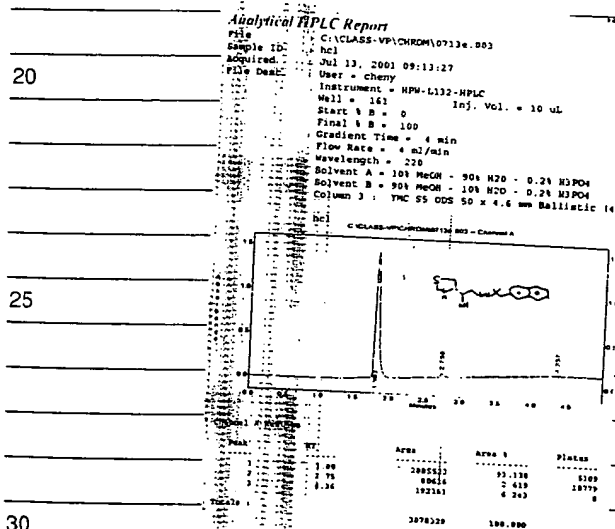


5
 48255-104-14 803 mg
 HCl in dioxane 20 ml
 THF 10 ml

10
 To a solution of 48255-104-14 in THF at RT was added 4N HCl in dioxane. The reaction was stirred at RT for 24 hr. Then evaporated to dryness. The residue was dissolved in sat'd NaHCO₃, EtOH was added and the organic layer was washed with brine and dried over MgSO₄. Evaporation gave a pale-yellow oil.

48255-105-14

15
¹H NMR were consistent, RQ
¹³C NMR



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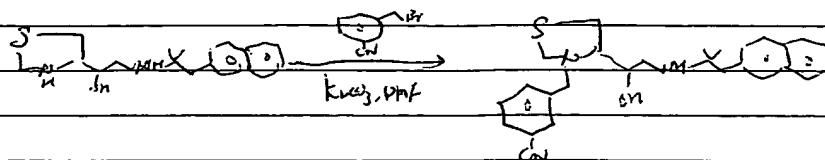
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08 Oct 7

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5	48255-105-14	100 mg	0.3 mmol
	2-bromotoluene	60 mg	0.3 mmol
	K ₂ CO ₃	46 mg	0.3 mmol
	DMF	2 ml	

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10 The mixture of 48255-105-14, 2-bromotoluene and K₂CO₃ in DMF was stirred at 40°C for 5 hr, then cooled to RT, stirring was continued overnight (3 days). Et₂O was added to the reaction and the solution was washed with H₂O (two times), brine and dried over MgSO₄. Purification was performed by flash chromatography on silica gel, loaded with CMC, eluted with 8% C₂H₅OH in CH₂Cl₂ with 0.2% NH₄OH. Pure fractions were combined and evaporated to give a white foam.

15 HPLC showed small impurities. Purified again by flash column, loaded with CMC, eluted with 12% C₂H₅OH in Et₂O. Pure fractions were combined and evaporated to give a foam.

20 48255-108-1a
48255-108-1a was dissolved in CH₂Cl₂. Et₂O (10 ml) was added. The mixture was stirred at RT for 30 min then evaporated to dryness. 120 mg
48255-108-2a

25 RQ 23496
MS (Mumukshu)
MS (Alicia)
EA
OK
30 PKC

35

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ATTACHMENT I

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